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(54) Title: COMPOSITIONS FOR THE TREATMENT OF MIGRAINE, CONTAINING POTASSIUM, MAGNESIUM AND PYRIDOXINE

(57) Abstract

Compositions for the treatment and prevention of migraine or stress headaches wherein there is supplied a combination of potassium, magnesium and pyridoxine optionally in association with other nutrients and/or simple analgesics.

thought to occur as the blood supply to the brain is restricted. There is sometimes a reduction in urine flow.

Vision

A very common phenomenon is the visual corona which registers upon the retina, often taking the form of a sparkling coloured zigzag "halo" which distorts the vision. Another visual signal can be patches of distortion within the field of vision (somewhat akin to looking through a rain splattered pane of glass). Some people develop acute sensitivity to light, or other less common visual symptoms.

Taste

Some sufferers experience a "sweet taste" upon their palate when no sugar is present, or some other taste distortion.

Hearing

Some sufferers experience tinnitus (ringing of the ears) or a certain loss of sound definition. Sometimes there is acute sensitivity to sound.

Touch

Some experience "tingling" sensations often in the face and extremities, some lose feeling altogether (paraesthesia - temporary paralysis).

Other Symptoms

Dizziness, loss of balance, nausea, vomiting, sugar craving, stomach pain, sudden fatigue or sudden irritability with no apparent cause, are also premonition symptoms.

Whatever form of early warning occurs, there follows a second stage of the attack. It may follow on immediately or after a hiatus period when no symptoms of any kind are

experienced until the second stage commences. This "rest period" usually lasts from 10 minutes up to an hour but can last up to 24 hours.

Once the attack enters the second stage, all of the early warning symptoms can develop further, almost always accompanied by extreme head pain. Some people have to lie in a darkened room, excluding all light and any movement to quell pain and vomiting.

This second stage can have a duration of a few hours or several days.

While the sensory disorientation experienced by migraine suffers appears to be a direct effect of impaired blood supply to the relevant receptors within the brain, other migraine symptoms correlate with the stages of stress response. I therefore conclude that the migraine cycle and the stress response are closely related.

One medical response to migraine is to attempt to eliminate the cause of migraine (if this is known). This is most easily ascertained if the cause is a definite food allergy such as cheese, wine or chocolate but this approach is not often successful.

If elimination proves unsuccessful then the only medical alternative is pain control or drug therapy to try to block the occurrence of migraine by drugs which act on neurotransmitters associated with stress such as serotonin and catecholamines or by analgesics. The pain of migraine is very difficult to eradicate. The strongest drugs commonly prescribed for migraine have to be given at near toxic levels to be at all efficacious. Most drugs, administered in "safe" doses are unable to completely relieve head pain. Even with the best of modern therapy many patients obtain only partial relief from their attacks.

The Invention

The invention is set out in the claims herein but simply stated the inventor has devised a method of treating migraine which involves the supply of three key ingredients, potassium, magnesium and pyridoxine. These three ingredients are effective alone but optionally may be combined with other nutrients and/or simple analgesics. Whether or not the theory on which the formulation is based is correct, the inventor has found this approach to be effective in treating migraine.

The present invention thus in one aspect provides a composition for use in combating by preventing or treating the effects of migraine and/or stress, said composition comprising potassium, Vitamin B_6 and magnesium, as essential ingredients. Optionally these three essentials may be combined with other nutrients and/or simple analgesics.

The term "composition" is used herein to include separate formulations which are intended for co-administration, either sequentially or simultaneously. It is generally more convenient however for the composition to be in a single admixture formulation.

In one embodiment, the composition comprises the active ingredients in amounts as follows, provided in the form of any appropriate salt or other derivative as well known to those skilled in the art:

Potassium	10 mg to 5000 mg, preferably 100 mg to 1000 mg and very preferably 300 mg to 600 mg.

Vitamin B_6	0.1 to 200 mg, preferably 1 mg to 100 mg and very preferably from 4 mg or 5 mg up to 30 mg.
and	
Magnesium	1.0 to 1000 mg, preferably 10 mg to 500 mg, very preferably 20 mg to 300 mg.

The composition may provide the three primary active ingredients alone or may provide these three together with other minerals and vitamins important in the stress response including calcium, phosphorus, iron, iodine and the water soluble vitamins vitamin B_1, vitamin B_2, vitamin B_3, vitamin B_5, vitamin B_{12}, folic acid, biotin, bioflavonoids and vitamin C. Optionally said composition may further comprise therapeutically effective amounts of copper, manganese and/or zinc. Tryprophan, which is a precursor of serotonin, which may be depleted in a migraine attack may also be included, preferably without other amino acids.

The formulation preferably does not contain any fats or fat soluble vitamins or alternatively it may omit carbohydrates other than excipients and sweeteners; it is certainly not in any sense nutritionally complete and is thus not intended as a supplement for nutritional purposes.

Simple analgesics which may be included in the formulation include aspirin (10 - 2000 mg), paracetamol (acetaminophen) (10 - 2000 mg), ibuprofen (10 - 2000 mg) or any non-steroidal anti-inflammatory drug.

The compositions according to the invention may be administered in any convenient form known to those skilled in the art. These forms include capsules of various types, powders, effervescent formulations, tablets, solutions, suspensions, emulsions and also aerosol sprays. The compositions may be administered orally, enterally, parenterally or transdermally using appropriate technology known to those skilled in the art.

In a further aspect, the present invention provides the use of a vitamin and mineral combination, or the use of any one or two of the components of the combination when for co-administration with the other(s) whether sequentially or simultaneously, in the manufacture of a medicament to combat migraine and/or stress, said combination comprising therapeutically effective amounts of potassium, vitamin B_6 and magnesium. Further ingredients may be optionally included as described above, for example the composition may include an analgesic.

In a yet further aspect, the present invention provides a method of combating migraine, and/or stress in a person subject to the same, said method comprising administering to said person a composition as described above, the components being given sequentially or simultaneously.

The active ingredients of the composition may be present in combination with any pharmaceutically acceptable carrier and may be in any assimilable form as well known to those skilled in the art for any particular ingredient. One possible carrier is water and in a preferred embodiment the composition is in the form of a tablet which effervesces when placed into water to produce aqueous solution which is then swallowed by the patient. Emulsions and flavoured solutions or suspensions are also possible formulations.

This formula has been tested in volunteer migraine sufferers. When the formula is taken as soon as any premonition symptoms are experienced, many sufferers do not develop the full scale migraine attack they are expecting.

These studies also have demonstrated that the formula, even when it contains no analgesics whatsoever, has a beneficial effect, even if taken after the stage of migraine pain is reached. In some cases, it removed all symptoms, with the exception of a "mild" headache, or greatly reduced the expected severity. For others it completely cleared all symptoms.

The study to date has demonstrated that 70% of the volunteers experienced full relief from debilitating migraine symptoms. A further 20% experienced partial relief, i.e. a reduction of all symptoms except for a mild headache, and for 10% the remedy appeared to have no effect. A number of the volunteers in the 20% partial success category appear to suffer from migraine in the form in which it has few if any premonition symptoms. As a result they were unable to determine when an attack was imminent and could not take the remedy at the optimum time, i.e. before head pain commenced. For those who experience this type of attack, called "common migraine", it is considered that the addition of a simple analgesic would be particularly beneficial.

Examples

There follow examples of formulas incorporating the invention, the particular form of the actives being merely for illustration. Any appropriate form as well known to those skilled in the art may be used. All figures are in mg and represent a unit dosage form which should be taken as early as possible during an attack. If relief is not obtained within 2 hours, a second dose may be taken, and further doses may be taken later.

	1	2	3	4	5	6
Potassium (e.g. as chloride or sulphate)	400	450	350	600	470.0	470.0
Magnesium (e.g. as citrate)	20	30	30	40	2.5	10
Pyridoxine	20	20	15	30	5	10
Calcium (e.g. as citrate)	-	-	-	-	25.0	60.0
Phosphorus (e.g. as dicalcium phosphate)	-	-	-	-	22.5	27.0
Iron (e.g. as sulphate)	-	-	-	-	0.625	0.1
Copper (e.g. as sulphate)	-	-	-	-	0.05	0.5
Zinc (e.g. as citrate)	-	-	-	-	0.25	0.001
Manganese (e.g. as gluconate)	-	-	-	-	0.25	-
Iodine (e.g. as potassium iodide)	-	-	-	-	-	0.15

To the formula may also be added other vitamins or nutrients such as the following (all figures are in mg):

Vitamin B_1	7.5	5.0
Vitamin B_2	2.5	5.0
Vitamin B_3	25.0	25.0
Vitamin B_5	5.0	10.0
Vitamin B_{12}	0.0025	0.035
Tryptophan	100	500
Folic Acid	0.15	0.2
Biotin	0.125	0.002
Vitamin C	75.0	60.0
Bioflavonoids	5.0	10.0

To any of the formulae illustrated above, analgesics may be added such as 1000 mg of aspirin or 1000 mg of ibuprofen or 800 mg of paracetamol. The minerals, vitamins and

analgesic may all be presented together or as different components within the same overall package.

As noted above the compositions of the invention are not full dietary supplements or nutritionally complete and the composition claims below do not extend when analgesics are absent to the many published instances of such, comprising besides the minerals and vitamins of the invention many other components and in particular fats, fatty acids and/or fat soluble vitamins.

A specific example is the following two-part formulation, one tablet of each kind:

a) Effervescent Mineral Tablet

Potassium chloride	600 mg
Potassium bicarbonate	400 mg
Anhydrous citric acid	800 mg

providing : 470 mg potassium; 285 mg chloride; 787.5 mg citrate

This was tested successfully at full strength and half strength (full strength listed above). A small proportion of sodium salts was present (sodium 2.6 mg).

b) Multi-vitamin Tablet

Magnesium sulphate
Pyridoxine hydrochloride
Phosphorus as dicalcium phosphate
Iron sulphate
Copper sulphate

Zinc sulphate

Manganese sulphate

Iodine as potassium iodide

B_1 Thiamine mononitrate

B_2 Riboflavin

B_3 Nicotinamide

B_5 pantothenic acid

B_{12} cyanocobalamin

Tryptophan

Folic acid

Biotin

Vitamin C as ascorbic acid

Bioflavonoids

The multi-vitamin tablets give the recommended daily intake of components having such recommendation, and in particular 8 mg magnesium and 7.5 mg pyridoxine. Rapid uptake of the potassium was aided by the effervescence of the mineral tablets.

Claims

1. A pharmaceutical preparation which provides 10 - 5000 mg of assimilable potassium, 0.1 to 300 mg of pyridoxine (vitamin B_6) and 1 - 1000 mg of assimilable magnesium.

2. A preparation for preventing or treating migraine or stress headaches, providing in effective amounts assimilable potassium, pyridoxine and assimilable magnesium, the amounts preferably being as set out in claim 1.

3. The preparation of claim 1 or 2 when in separate formulations each comprising one or two of the actives, for sequential or simultaneous co-administration.

4. The use of a vitamin and mineral combination, or of any one or two of its components when for sequential or simultaneous co-administration with the other(s), in the manufacture of a medicament to prevent or treat migraine or stress headaches, said combination providing in effective amounts assimilable potassium, pyridoxine and assimilable magnesium, the amounts preferably being as set out in claim 1.

5. A method of preventing or treating migraine or stress headaches by administrating, separately or simultaneously, effective amounts of assimilable potassium, pyridoxine and assimilable magnesium, the amounts preferably being as set out in claim 1.

6. As claims 1 - 5, particularly for preventing or treating migraine by administration at the premonition or early warning stage of an attack.

7. As claims 1 - 6 but with the addition in assimilable form of effective amounts of other minerals and vitamins selected from calcium, phosphorus, iodine, iron, copper,

zinc, manganese, tryptophan, folic acid, biotin, bioflavonoids and vitamins B_1, B_2, B_3, B_5, B_{12} and C.

8. As claims 1 - 7 but with the addition of an effective dose of an analgesic or non-steroidal anti-inflammatory drug such as aspirin, paracetamol or ibuprofen.

AMENDED CLAIMS
[received by the International Bureau on 24 June 1997 (24.06.97); original claims 1,4 and 8 amended; new claim 9 added; remaining claims unchanged (2 pages)]

1. A pharmaceutical preparation which provides 10 - 5000 mg of assimilable potassium, 0.1 to 300 mg of pyridoxine (vitamin B_6) and 1 - 1000 mg of assimilable magnesium, said potassium and magnesium being in a form other than the aspartate salt.

2. A preparation for preventing or treating migraine or stress headaches, providing in effective amounts assimilable potassium pyridoxine and assimilable magnesium, the amounts preferably being as set out in claim 1.

3. The preparation of claim 1 or 2 when in separate formulations each comprising one or two of the actives, for sequential or simultaneous co-administration.

4. The use of a vitamin and mineral combination, or of any one of or two of its components when for sequential or simultaneous co-administration with the other(s), in the manufacture of a medicament to prevent or treat migraine or stress headaches, said combination providing in effective amounts assimilable potassium, pyridoxine and assimilable magnesium, the amounts preferably being as set out in claim 1.

5. A method of preventing or treating migraine or stress headaches by administering, separately or simultaneously, effective amounts of assimilable potassium, pyridoxine and assimilable magnesium, the amounts preferably being as set out in claim 1.

6. As claims 1 - 5, particularly for preventing or treating migraine by administration at the premonition or early warning stage of an attack.

7. As claims 1-6 but with the addition in assimilable form of effective amounts of other minerals and vitamins selected from calcium, phosphorus, iodine, iron, copper, zinc, manganese, tryptophan, folic acid, biotin, bioflavonoids and vitamins B_1, B_2, B_3, B_5, B_{12} and C.

8. As claims 2-7 but with the addition of an effective dose of an analgesic or non-steroidal anti-inflammatory drug such as aspirin, paracetamol or ibuprofen.

9. A pharmaceutical preparation which provides 10 - 5000 mg of assimilable potassium, 0.1 to 300 mg of pyridoxine (vitamin B_6) and 1 - 1000 mg of assimilable magnesium, together with an effective dose of an analgesic or non-steroidal anti-inflammatory drug such as aspirin, paracetamol or ibuprofen.

INTERNATIONAL SEARCH REPORT

Int .onal Application No
PCT/GB 97/00213

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/06 //(A61K33/06,33:00,31:44)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WIEN.MED.WSCHR., 1976, 126/24 (354-356), AUSTRIA, XP000647007 ARGYROPOULOS G. ET AL: "Alleviation of pain by infusions in neurological and neurosurgical patients" see page 355, column 1 see page 355, column 2, paragraph 5 ---	1
X	FR 3 022 M (LABORATOIRES BIOSEDRA) 21 December 1964 see claims ---	1
A	WO 94 27449 A (HAMILTON DONALD SINCLAIR) 8 December 1994 see abstract --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 1997	24.04.1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/GB 97/00213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 582 705 A (PRIMES LEONARD ET AL) 15 April 1986 see column 6; example 9	1-8

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ional Application No
PCT/GB 97/00213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 3022 M		NONE	
WO 9427449 A	08-12-94	AU 676314 B	06-03-97
		AU 6584494 A	20-12-94
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US 4582705 A	15-04-86	NONE	